REMARKS

Applicants respectfully request favorable reconsideration in view of the herewith presented amendments and remarks.

Claims 1-33 are pending in this application. Please cancel claims 2, 3, and 12 without prejudice. Claims 19-28 and 30-33 are withdrawn from consideration as being directed to non-elected inventions. Claims 1-18 and 29 are rejected. Applicants reserve the right to file a divisional or continuation application directed to the subject matter that has been cancelled or withdrawn herefrom.

Claims 1 and 13 have been amended to include the phrase "physiologically- suitable polypeptide carrier selected from the group consisting of: a bacterial toxin, toxoid, and bacterial or viral polypeptide" as supported by the instant specification at page 11, lines 10-22. Claim 1 has been further amended to clarify the molecular weight range.

No new matter has been introduced by these amendments.

35 U.S.C. §112, First Paragraph

26. Claims 1, 4-18, and 29 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicants respectfully disagree with the Examiner's contention that the added elements of claims 1, 4-18, and 29, hyaluronic acid "moieties" and/or "immunogenic conjugate induces an immune response to epitopes comprising the non-reducing terminal glucuronic acid or unsaturated glucuronic acid residues of said hyaluronic acid moieties" is not supported by the instant specification and presents new matter. The Examiner's attention is respectfully directed to page 6, lines 13-23 of the instant specification which describes a hyaluronic acid useful for eliciting an immune response, where the epitope that is cross-reactive with group A and group C streptococci is located at the non-reducing terminal glucuronic acid or unsaturated glucuronic acid of the hyaluronic acid. Furthermore, one skilled in the art would understand that hyaluronic

acid moieties refer to a "part, portion or share" of the hyaluronic acid or the poly-glucaronic acid portion. The claims as previously amended do not introduce new subject matter. Applicants respectfully request reconsideration and withdrawal of this §112, first paragraph rejection.

35 U.S.C. §112, Second Paragraph

27. Claims 12, 13, 17, 18, and 29 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

(a) The Examiner has rejected Claim 13 for lacking proper antecedent basis for the recitation "hyaluronic acid moieties." Applicants respectfully disagree with this rejection. However, where appropriate, applicants have amended claim 13 to recite - -the hyaluronic acid moieties- - in order to comply with the Examiner's concerns.

(b) Claims 12, 17, 18, and 29 stand rejected for being improperly dependent, directly or indirectly, from a cancelled claim. Applicants have amended claims 12, 17, and 29 such that the claims are now in proper dependent format.

Applicants respectfully request reconsideration and withdrawal of this §112, second paragraph rejection.

35 U.S.C. §103

28. Claims 1, 4-10, and 13-16 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Fillit, et al. (1986), in view of Kazuo, et al. (JP 9012600), Nebinger, et al. (Nebinger, et al., 1983), or Nebinger, 1985, or Shimada, et al. (J. Biochem (Tokyo) 96:721-725, 1984), or Ulrich, et al. (*Hoppe-Seyler's Z. Physiol. Chem.* 360:1457-1463, 1979, abstract) and Kazuo, et al. and Fillit, et al. (Fillit, et al. 1986). In order to expedite prosecution of this application, applicants have amended the claims to encompass an immunologically- and physiologically-suitable polypeptide carrier selected from the group consisting of: a bacterial toxin, toxoid, and bacterial or viral polypeptide having the percent glucuronic acid content of the hyaluronic acid (HA) and the molecular weight of the HA as presently stated in claim 1. There is no motivation or guidance in the cited publications for one skilled in the art to construct the

claimed conjugate molecule. Further, the Examiner has used hindsight to amass the cited art (which does not teach or make obvious applicants' invention) as there is no motivation to combine these particular references in this particular fashion. Applicants respectfully traverse this rejection.

The Examiner contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace the large hyaluronate in Fillit's (1988) conjugate with Nebbinger's (1983 or 1985) decasaccharides or octasaccharides, or Shimada's hyaluronic acid oligosaccharides, or Ulrich's hyaluronic acid tetrasaccharides, and replace Fillit's phosphatidylethanolamine with Kazuo's protein to produce the instant invention with a reasonable expectation of success. However, to establish a *prima facie* case of obviousness, three basic criteria must be met [MPEP 2143]. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, (Fed. Cir. 1991).

The combination of Fillit, et al. (1986 or 1988), Kazuo, et al., Nebinger, et al. (1983 or 1985), Shimada, et al., and Ulrich, et al., fails to teach or suggest all of the claim elements. There is no teaching or suggestion in the combination of references of a conjugate molecule comprising a polysaccharide or oligosaccharide that is covalently bound to an immunoligically- and physiologically- suitable bacterial toxin, toxoid, or bacterial or viral polypeptide carrier as claimed in the instant invention having the claimed glucuronic content percentage. Fillit (1988) reports of a polysaccharide or oligosaccharide mixed and bound to liposomes and refers to the Fillit (1986) publication.

Fillit (1986) provides a method of conjugating hyaluronic acid (HA) to BSA in preparation for ELISA assays; however, HA is not covalently bound to BSA. Briefly, soluble HA was prepared from streptococcal HA (group C) by sonication. Benzoquinone (benzene ring

with 2 keto groups in para position, i.e., 1,4) was then reacted with the soluble HA, assuming that the reaction would occur through the hydroxyl groups on the sugars. However, only the amino groups of HA would react with benzoquinone since the hydroxyl groups are not sufficiently nucleophilic to produce a chemically bonded adduct. Instead, a polysaccharide-benzoquinone complex would form through electrostatic and/or hydrophobic (Van der Vaals) interactions. The benzoquinone of the polysaccharide-benzoquinone complex was then reacted with the amino groups of BSA. However, the interaction between the complex and BSA is not covalent, but rather an unstable reversible Schiff base is most likely formed. Therefore, the resulting "conjugate" of Fillit does not form a covalent complex since the link between the polysaccharide and benzoquinone is not covalent and the bond between the polysaccharide-benzoquinone complex and BSA is unstable and reversible to free components.

Similarly, the Fillit (1988) publication is directed to a polysaccharide-benzoquinone complex that is not covalently bonded to a liposome. Specifically, when reacting the phosphatidylethanolamine and the polysaccharide-benzoquinone complex, the resulting linkage is through an unstable and reversible Schiff base. The Fillit liposome conjugate does not form a covalent bond as claimed in the instant application. The Fillit, et al. publications simply report the immunogenicity of HA in rabbits. Neither publication teaches or suggests an HA conjugate covalently bound to a bacterial toxin, toxoid, or bacterial or viral polypeptide carrier with the purpose of treating or preventing bacterial infections in mammals. The Kazuo abstract also does not teach or provide guidance for the skilled artisan to prepare the claimed conjugate.

Although the Kazuo abstract reports of a hyaluronate and protein conjugate, there is no guidance or teaching as how one skilled in the art would prepare the claimed conjugate comprising a polysaccharide or oligosaccharide covalently bound to an immunologically- and physiologically- suitable bacterial toxin, toxoid, or bacterial or viral polypeptide carrier. The Kazuo abstract reports conjugating the hyaluronate to a protein such as hemocyanin or a phospholipid. However, hemocyanin is not an appropriate carrier for humans and the Kazuo publication does not provide guidance for one skilled in the art to specifically select the bacterial toxin, toxoid, or bacterial or viral polypeptide as a carrier. Claim 1 has been amended and is directed to a conjugate molecule comprising a polysaccharide or oligosaccharide covalently

bound to an immunologically- and physiologically- suitable polypeptide selected from the group consisting of: a bacterial toxin, toxoid, or bacterial or viral polypeptide carrier. The claimed conjugate also comprises greater than 50% of the hyaluronic acids of the claimed hyaluronic acid conjugates have a non-reducing terminal glucuronic acid and/or unsaturated glucuronic acid residue which induce an immune response and that the hyaluronic acid moieities are low molecular weight hyaluronic acid with a molecular weight ranging from about 600 daltons and about 400 kilodaltons. There is no teaching or suggestion in the combination of the references of such an immunogenic conjugate.

In fact, the Fillit, et al. (1988) publication reports of a hyaluronic acid having a molecular weight of 15,000 kilodaltons, much greater than the claimed hyaluronic acid having a molecular weight ranging between 600 daltons to 400 kilodaltons, is silent with respect to the percentage of hyaluronic acid moieties having a non-reducing terminal glucuronic acid and/or unsaturated glucuronic acid residue. The Examiner contends that it would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the phosphatidylethanolamine with Kazuo's hemocyanin to produce the claimed immunogenic conjugate.

Ulrich, et al. does not teach or suggest a conjugate comprising a hyaluronic acid and an immunologically- and physiologically- suitable bacterial toxin, toxoid, or bacterial or viral polypeptide carrier. Ulrich, et al. simply reports degrading even-numbered oligosaccharides from hyaluronic acid with either D-glucuronic acid or N-acetylglucosamine using specific lyases and does not teach or provide any motivation for the skilled artisan to construct a low molecular weight hyaluronic acid that is covalently bound to a bacterial toxin, toxoid, or bacterial or viral polypeptide carrier.

Neither does Shimada, et al. teach or suggest the claimed conjugate. Shimada, et al. reports a thin-layer chromatographic analysis of hyaluronate oligosaccharides. The cited publication further reports separating even-numbered and odd-numbered oligosaccharides by thin-layer chromatography (TLC). However, Shimada, et al. does not provide any guidance as to how the skilled artisan would prepare immunogenic conjugate molecules comprising hyaluronic

acid covalently bound to an immunologically- and physiologically- suitable bacterial toxin, toxoid, or bacterial or viral polypeptide carrier.

The combination of publications as relied on by the Examiner, however, is improper because they do not themselves provide any motivation for their combination. The mere fact that the Examiner can combines or modifies the references does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F.2d 680 (Fed. Cir. 1990). One skilled in the art would have no motivation to construct the claimed immunogenic conjugate comprising hyaluronic acid covalently bound to an immunologically- and physiologically- suitable bacterial toxin, toxoid, or bacterial or viral polypeptide carrier. Several different polysaccharide carriers may be used in preparing conjugate molecules, but none of the cited publications teach or suggest a bacterial toxin, toxoid, or bacterial or viral polypeptide carrier. In fact, one skilled in the art would not have sufficient guidance in selecting a bacterial toxin, toxoid, or bacterial or viral polypeptide carrier, especially since none of the publications teach using the conjugate for treating infectious diseases. None of these references, either alone or in combination with the cited references, teaches the specifically claimed conjugate.

The Examiner further contends that one skilled in the art would have been motivated to produce the instant invention by reducing the viscosity of Fillit's (1988) large hyaluronic acid so that the product becomes more manageable with the hidden antigenic sites of terminal glucuronic acid advantageously exposed as taught by Fillit, et al. (1986). Regardless of size, the Fillit, et al. publication does not teach or suggest a covalently bound conjugate molecule as claimed in the instant application.

Therefore, Fillit, et al. (1986 or 1988), Kazuo, et al., Nebinger, et al. (1983 or 1985), Shimada, et al., and/or Ulrich, et al., neither alone or in combination, teach, suggest, or obviate to one skilled in the art the immunogenic conjugate molecules comprising hyaluronic acid covalently bound to an immunologically- and physiologically- suitable bacterial toxin, toxoid, or bacterial or viral polypeptide carrier as claimed in the instant application. Therefore, in light of the amendments and arguments presented above, applicants respectfully request reconsideration and withdrawal of this §103 rejection.

29. Claim 11 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Fillit, et al. (1988) as modified by Kazuo, et al., Nebinger, et al. (1983 or 1985), or Shimada, et al., or Ulrich, et al., and Kazuo, et al. and Fillit, et al. (1986) as applied to claim 1, and further in view of Blake, et al. and Philip, et al. Applicants respectfully disagree with this rejection. However, in order to expedite prosecution of this application, applicants have amended claim 1 by replacing a "polypeptide" carrier with a "bacterial toxin, toxoid, and bacterial or viral polypeptide" carrier.

As previously discussed, Fillit, et al. (1988) as modified by Kazuo, et al., Nebinger, et al. (1983 or 1985), or Shimada, et al., or Ulrich, et al., and Kazuo, et al. and Fillit, et al. (1986) do not teach or suggest the claimed conjugate. Applicants further traverse the ground of rejection as Blake, et al. merely provides porin as another example of a bacterial carrier protein. Blake, et al. and Swain, et al. simply provide examples of other protein carriers, neither of which motivate one to select a bacterial toxin, toxoid, or bacterial or viral polypeptide carrier. Thus, reconsideration and withdrawal of this 35 U.S.C. §103(a) rejection is respectfully requested.

CONCLUSION

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for the timely consideration of this amendment under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account No. 13-4500, Order No. 3842-4050.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition and for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 3842-4050. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: December 22, 2003

By: _____
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